EXHIBIT D

...ia may be more susceptible to systemic toxici-...ent doses due to their larger skin surface to ... (See PRECAUTIONS—Pediatric use).

...elops, DesOwen Cream, Ointment or Lotion ...ntinued and appropriate therapy instituted. ...ed dermatitis with corticosteroids is usually ...observing *failure to heal* rather than noting a ...ration as with most topical products not con...steroids. Such an observation should be cor...h appropriate diagnostic patch testing.

...skin infections are present or develop, an ...ntifungal or antibacterial agent should be ...opriate response does not occur promptly, use of ...onide cream, ointment and lotion) Cream, ...Lotion should be discontinued until the infec... adequately controlled.

...for patients: Patients using topical corticoste... receive the following information and instruc...

...otion is to be used as directed by the physician. ...ternal use only. Avoid contact with the eyes. ...tion should not be used for any disorder other ...for which it was prescribed.

...kin area should not be bandaged or otherwise ...wrapped so as to be occlusive unless directed by ...ian.

...ould report to their physician any signs of local ...ctions.

...ories: The following tests may be helpful in ...tients for HPA axis suppression:

...mulation test

...ma cortisol test

...ne cortisol test

...s, mutagenesis, and impairment of fertility: ...nimal studies have not been performed to evalu... mutagenic potential or the effect on reproduction ...of DesOwen Cream, Ointment, and Lotion.

...ratogenic effects: *Pregnancy category C*: ...s have been shown to be teratogenic in laborat... when administered systemically at relatively ...ls. Some corticosteroids have been shown to ...after dermal application in laboratory ani... reproduction studies have not been conducted ...n Cream, Ointment or Lotion. It is also not ...er DesOwen Cream, Ointment or Lotion can ...m when administered to a pregnant woman or ...roduction capacity. DesOwen Cream, Oint...ion should be given to a pregnant woman only if ...ed.

...ers: Systemically administered corticoste... in human milk and could suppress growth, in...dogenous corticosteroid production, or cause ...r effects. It is not known whether topical ad... of corticosteroids could result in sufficient sys...ion to produce detectable quantities in human ...Many drugs are excreted in human milk, cau... exercised when DesOwen Cream, Ointment or ...inistered to a nursing woman.

...Safety and effectiveness in pediatric patients ...e established. Because of a higher ratio of skin ...to body mass, pediatric patients are at a greater ...ects of HPA axis suppression when they are ...topical corticosteroids. They are therefore also ...of glucocorticosteroid insufficiency after with... ...ment and of Cushing's syndrome while on ...verse effects including striae have been re... ...inappropriate use of topical corticosteroids in ...ldren.

...pression, Cushing's syndrome, linear growth ...delayed weight gain and intracranial hyperten... reported in children receiving topical cortico... ...estations of adrenal suppression in children ...ma cortisol levels, and absence of response to ...tion. Manifestations of intracranial hyperten...ulging fontanelles, headaches, and bilateral ...

...EACTIONS

...clinical trials, the total incidence of adverse ...ted with the use of desonide was approxi... were: stinging and burning approximately ...ontact dermatitis, condition worsened, peel...ing, intense transient erythema, and dry... each less than 2%.

...Additional local adverse reactions have been ...ently with other topical corticosteroids, and ...more frequently with the use of occlusive ...ially with higher potency corticosteroids ...are listed in an approximate decreasing or... folliculitis, acneiform eruptions, hypopig...tal dermatitis, secondary infection, skin ...and miliaria.

...of DesOwen (desonide cream, ointment, ...m, Ointment and Lotion can be absorbed in sufficient amounts to produce systemic effects (See PRECAUTIONS).

DOSAGE AND ADMINISTRATION

DesOwen Cream, Ointment or Lotion should be applied to the affected areas as a thin film two or three times daily depending on the severity of the condition. SHAKE LOTION WELL BEFORE USING.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. DesOwen Cream, Ointment and Lotion should not be used with occlusive dressings.

HOW SUPPLIED

DesOwen (desonide cream) Cream 0.05% is supplied in tubes containing:

15 g NDC 0299-5770-15
60 g NDC 0299-5770-60
90 g NDC 0299-5770-90

DesOwen (desonide ointment) Ointment 0.05% is supplied in tubes containing:

15 g NDC 0299-5775-15
60 g NDC 0299-5775-60

DesOwen (desonide lotion) Lotion 0.05% is supplied in bottles containing:

2 fl oz NDC 0299-5765-02
4 fl oz NDC 0299-5765-04

Storage Conditions: Store between 2° and 30°C (36° and 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Marketed by:
Galderma Laboratories, Inc.
Fort Worth, Texas 76133, USA
Mfd. by: DPT Laboratories, Inc
San Antonio, Texas 78215, USA
GALDERMA is a registered trademark.
225025-0396 Revised: March 1996

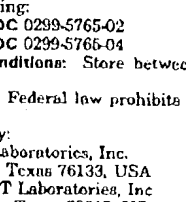
METROGEL®

(metronidazole topical gel)
0.75% Topical Gel
FOR TOPICAL USE ONLY
(NOT FOR OPHTHALMIC USE)

R

DESCRIPTION

METROGEL® Topical Gel contains metronidazole, USP, at a concentration of 7.5 mg per gram (0.75%) in a gel consisting of purified water, methylparaben, propylparaben, propylene glycol, carbomer 940, sodium hydroxide, and edetate disodium. Metronidazole is classified therapeutically as an antiprotozoal and anti-bacterial agent. Chemically, metronidazole is named 2-methyl-5-nitro-1*H*-imidazole-1-ethanol and has the following structure:



CLINICAL PHARMACOLOGY

Bioavailability studies on the topical administration of 1 gram of METROGEL Topical Gel to the face (7.5 mg of metronidazole) of 10 rosacea patients showed a maximum serum concentration of 66 nanograms per milliliter in one patient. This concentration is approximately 100 times less than concentrations afforded by a single 250 mg oral tablet. The serum metronidazole concentrations were below the detectable limits of the assay at the majority of time points in all patients. Three of the patients had no detectable serum concentrations of metronidazole at any time point. The mean dose of gel applied during clinical studies was 600 mg which represents 4.5 mg of metronidazole per application. Therefore, under normal usage levels, the formulation affords minimal serum concentrations of metronidazole. The mechanisms by which METROGEL (metronidazole topical gel) Topical Gel acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

INDICATIONS AND USAGE

METROGEL Topical Gel is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

CONTRAINDICATIONS

METROGEL Topical Gel is contraindicated in individuals with a history of hypersensitivity to metronidazole, parabens, or other ingredients of the formulation.

PRECAUTIONS

General: METROGEL Topical Gel has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of blood dyscrasia.

Information for patients: This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

Drug Interactions: Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

Carcinogenesis, mutagenesis, impairment of fertility: Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters.

Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injections and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200–1200 mg/day of metronidazole for 1 to 24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

Pregnancy: *Teratogenic effects: Pregnancy category B:* There has been no experience to date with the use of METROGEL (metronidazole topical gel) Topical Gel in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

Nursing mothers: After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though METROGEL Topical Gel blood levels are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The following adverse experiences have been reported with the topical use of metronidazole: burning, skin irritation, dryness, transient redness, metallic taste, tingling or numbness of extremities and nausea.

DOSAGE AND ADMINISTRATION

Apply and rub in a thin film of METROGEL Topical Gel twice daily, morning and evening, to entire affected areas after washing.

Areas to be treated should be cleansed before application of METROGEL (metronidazole topical gel) Topical Gel. Patients may use cosmetics after application of METROGEL Topical Gel.

HOW SUPPLIED

METROGEL (metronidazole topical gel) Topical Gel is supplied in a 1 oz. (28.4 g) aluminum tube—NDC 0299-3835-28 and a 45 g aluminum tube—NDC 0299-3835-45.

Storage conditions: STORE AT CONTROLLED ROOM TEMPERATURE: 15° to 30°C (59° to 86°F).

Caution: Federal law prohibits dispensing without prescription.

GALDERMA

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